PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/00

A1

(11) International Publication Number: **WO 00/61110**

(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/KR00/00321

(22) International Filing Date: 7 April 2000 (07.04.00)

(30) Priority Data:
1999/12520 9 April 1999 (09.04.99) KR

(71) Applicant *(for all designated States except US)*: MOGAM BIOTECHNOLOGY RESEARCH INSTITUTE [KR/KR]; 341 Pojung-ri Koosung-myun, Yongin-shi, Kyonggi-do 449-910 (KR).

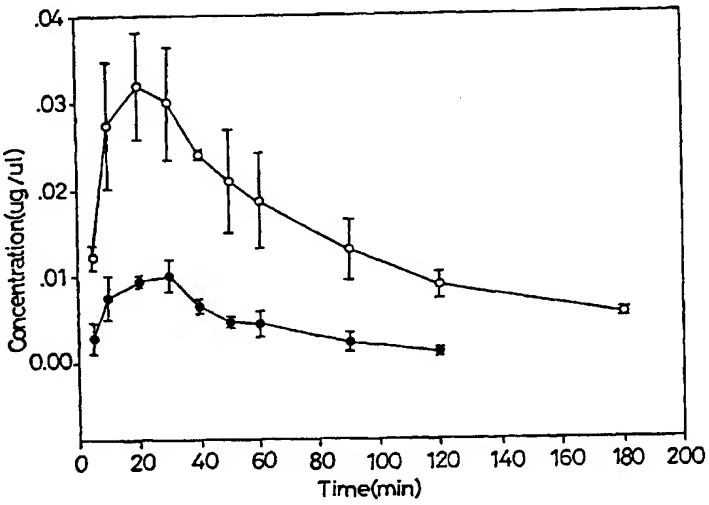
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HEO, Moon-Young [KR/KR]; 102-405 Green Town Apartment, Toegye-dong, Choonchon-shi, Kangwon-do 200-170 (KR). KIM, Hyun-Pyo [KR/KR]; 207-2301 Olympic Seonsoochon Apartment, 89 Bangi-dong, Songpa-ku, Seoul 138-050 (KR). CHEONG, Hong-Seok [KR/KR]; 1309-1402 Green Town Apartment, Joong 2-dong, Wonmi-ku, Bucheon-shi, Kyonggi-do 420-022 (KR).

(74) Agent: LEE, Han-Young; 8th Fl., Seowon Bldg., 1675-1 Seocho-dong, Seocho-gu, Seoul 137-070 (KR).

(81) Designated States: AU, CN, JP, RU, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
In English translation (filed in Korean).

(54) Title: ICECREAM-TYPE PHARMACEUTICAL FORMULATION AND PROCESS FOR PREPARING THE SAME



(57) Abstract

The present invention relates to a soft icecream-type pharmaceutical formulation and a process for preparing the same. The icecream-type pharmaceutical formulation of present invention is prepared by the steps of mixing egg yolk, milk, and cocoa with stirring until the cocoa is completely dissolved in the mixture; whipping a cream until it is reduced to pulp and mixing it with the said mixture in a volume ratio of 9:1 to 5:5; adding drugs into the said mixture and blending them; and, putting them into an ice cream maker and formulating into a pharmaceutical formula. Since a soft ice cream-type-formulation of the invention has merits over conventional formulas in terms of taking preference and absorbtion efficacy in oral application, it can be used as an improved pharmaceutical formula for children and infants, while substituting for troches.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

ICECREAM-TYPE PHARMACEUTICAL FORMULATION AND PROCESS FOR PREPARING THE SAME

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a soft icecream-type pharmaceutical formulation and a process for preparing the same.

Description of the Prior Art

Antipyretics, antibiotics and vitamins have been conventionally formulated in the forms of tablet, capsule, liquid, injection solution and syrup. The conventional dosage forms are, however, proven to be less satisfactory in the sense that they are not convenient for administering to children. Accordingly, particular attention should be paid in choosing the dosage forms, especially, orally administrable pharmaceutical formulations are selected under a careful consideration of taste and mouth feel in oral cavity.

Unfortunately, many medicines and active ingredients are bitter in taste or else hold uncomfortable taste, rough or chalky feeling. With the recent development in pharmaceutical technology, to improve taste and/or mouth feel in oral cavity, the pharmaceutical formulations of relatively easy administration for children such as chewable tablet, jelly-like tablet, granules, etc., have been developed. They are commercially available though these pharmaceutical formulations are not ideal in terms of children's affinity. Under the circumstances, there are strong reasons for exploring and developing new type of pharmaceutical formulation for children.

SUMMARY OF THE INVENTION

The present inventors have made efforts to develop an icecream-type pharmaceutical formulation which can be applied in drugs such as antipyretics, antibiotics and vitamins, and found that it provides excellent drug absorption with improved patient's drug compliance in light of easy oral application and high affinity.

The primary object of the present invention is, therefore, to provide an icecream-type pharmaceutical formulation.

The other object of the invention is to provide a process for preparing the icecream-type pharmaceutical formulation.

Another object of the invention is to provide icecream-type formulations of antipyretic, antibiotic and vitamin.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and the other objects and features of the present invention will become apparent from the following descriptions given in conjunction with the accompanying drawings, in which:

Figure 1 is a high performance liquid chromatography chromatogram of acetaminophen in blood.

Figure 2 is a graph showing blood level of tablet-type and icecream-type acetaminophen after oral administration.

DETAILED DESCRIPTION OF THE INVENTION

Icecream-type pharmaceutical formulation of the present invention is prepared by the steps of: mixing egg

yolk and milk with stirring until they are completely mixed; whipping cream until it is reduced to pulp and mixing it with the said mixture in a volume ratio of 9:1 to 5:5, more preferably 8:2 to 6:4, most preferably 7:3; adding drugs into the said mixture in a ratio of 0.1 to 20wt% and blending them; and, finally putting them into an icecream maker and formulating into a pharmaceutical formula by subjecting at the temperature range of 0°C to -10°C.

In the preparation of the icecream-type formulation, sugar and/or cocoa may be further added to the mixture of egg yolk and milk according to the patient's preference, and coconut hard fat may substitute for the egg yolk. Further, the milk includes soy bean milk, processed skim milk(containing 7.2% skimmed milk powder) and plain milk. And, the cream includes: commercially available emulsion cream which can be obtained by the centrifuge of animal/vegetable oil; and, carboxymethylcellulose(CMC) solution. Though several pharmaceutical formulations of antipyretics, antibiotics or vitamins are illustrated in the Examples below, they do not specifically limit the drugs contained in the formulation. The antipyretics include acetaminophen, aspirin, ibuprofen, ketoprofen and isopropyl-antipyrin, preferably acetaminophen and/or mixture thereofs, the antibiotics include amoxicillin, ampicillin, erythromycin, lincomycin, and cefalexin, most preferably amoxicillin, and the vitamins include retinol acetate, cholecalciferol, tocopherol acetate, ascorbic acid, thiamine nitrate, riboflamin, pyridoxine hydrochloride, nicotinamide and cyanocobalamin.

The present invention is further illustrated in the following examples, which should not be taken to limit the scope of the invention.

Example 1: Preparation of icecream-type formulation containing an antipyretic of acetaminophen

Example 1-1

Sugar, cocoa, egg yolk and milk were weighed in the ratios shown in Table 1 below, and mixed with stirring until they were completely dissolved. Then, commercially available emulsion cream was whipped until it was reduced to pulp and mixed with the said mixture. And then, acetaminophen, an antipyretic, was added to the mixture, blended, and put in an icecream maker(Philips, HR2034) and subjected at a temperature of 0℃ to -10℃, to give an icecream-type formula.

Table 1. The contents of icecream-type formulation containing acetaminophen

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Acetaminophen	0.20

Example 1-2

An icecream-type antipyretic formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients shown in Table 2 below.

Table 2. The contents of icecream-type formulation containing acetaminophen

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Acetaminophen	1.00

Example 1-3

An icecream-type antipyretic formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients shown in Table 3 below.

Table 3. The contents of icecream-type formulation containing acetaminophen

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Acetaminophen	10.00

Example 2: Preparation of icecream-type formulation containing an antibiotic of amoxicillin

Example 2-1

An icecream-type antibiotic formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients shown in Table 4 below.

Table 4: The contents of icecream-type formulation containing amoxicillin

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Amoxicillin	0.20

Example 2-2

An icecream-type antibiotic formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients shown in Table 5 below.

Table 5: The contents of icecream-type formulation containing amoxicillin

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Amoxicillin	1.00

Example 2-3

An icecream-type antibiotic formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients shown in Table 6 below.

Table 6: The contents of icecream-type formulation containing amoxicillin

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Amoxicillin	10.00

Example 3: Preparation of icecream-type formulation containing vitamins

Example 3-1:

An icecream-type multi-vitamin formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients of retinol acetate, cholecalciferol, tocopherol acetate, ascorbic acid, thiamine nitrate, riboflavin, pyridoxine hydrochloride, nicotinamide and cyanocobalamin as shown in Table 7 below.

Table 7: The contents of icecream-type formulation containing vitamins

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Retinol acetate	0.002
Cholecalciferol	0.0004
Tocopherol acetate	0.02
Ascorbic acid	0.04
Thiamine nitrate	0.0008
Riboflavin	0.0008
Pyridoxine hydrochloride	0.0012
Nicotinamide	0.008
Cyanocobalamin	0.000004

Example 3-2:

An icecream-type multi-vitamin formulation was prepared in an analogous manner as in Example 1-1, except for employing the ingredients of retinol acetate, cholecalciferol, tocopherol acetate, ascorbic acid, thiamine nitrate, riboflavin, pyridoxine hydrochloride, nicotinamide and cyanocobalamin as shown in Table 8 below.

Table 8: The contents of icecream-type formulation containing vitamins

Ingredients	Ratio(wt%)
Milk	*q.s.* 100.00
Sugar	18.00
Cocoa	3.60
Egg yolk	6.00
Emulsion cream	30.00
Retinol acetate	0.1
Cholecalciferol	0.02
Tocopherol acetate	1.0
Ascorbic acid	2.0
Thiamine nitrate	0.04
Riboflavin	0.04
Pyridoxine hydrochloride	0.06
Nicotinamide	0.4
Cyanocobalamin	0.0002

Example 4: Measurement of Blood Level of Drugs

To measure the blood level of acetaminophen, male SD rats were cannulized in arteriae femoralis after the ether treatment. When the rats were come out of the ether, commercially available acetaminophen tablet and icecream-type formulation were orally administered with an equal amount of 100mg/kgBW as acetaminophen per each. Blood was collected in an equal interval and injected to high performance liquid chromatography(HPLC) working under the analysis condition below. The HPLC chromatogram of acetaminophen in blood is shown in Figure 1.

Condition for HPLC Analysis:

Column: μ Bondapak C18(Waters, U.S.A.)
Mobile phase: acetonitrile : 1% acetate(1:9, v:v)
flow rate - 1ml/min
Detector: UV spectrophotometer (λ=254nm)

Example 5: Changes in Blood Level of Acetaminophen

Changes in blood level of acetaminophen were monitored by the method illustrated in Example 4, after oral administration of 50g icecream-type formulation prepared in Example 2-2(containing 500mg acetaminophen) and commercially available acetaminophen tablet(containing 500mg acetaminophen) in an amount of 100mg/kg to experimental rats(see: Figure 2). As shown in Figure 2, C_{max} for the icecream-type formulation containing acetaminophen(○) was shown at 20min while tablet form(●) was at 30min, and the blood level of drug in the icecream-type formulation was 3 times as high as the tablet-type formulation.

Example 6: Changes in Blood Level of Amoxicillin

Changes in blood level of amoxicillin were monitored by the method illustrated in Example 4, after oral administration of 50g icecream-type formulation prepared in Example 2-2(containing 500mg amoxicillin) and commercially available amoxicillin capsule(containing 500mg amoxicillin) in an amount of 10mg/kg to experimental rats.

As a result, it was clearly determined that both of the icecream-type formulation and capsule-type formulation of amoxicillin showed similar blood level curve.

Example 7: Changes in Blood Level of Tocopherol Acetate

Changes in blood level of tocopherol acetate were monitored by the method illustrated in Example 4, after oral administration of 50g icecream-type formulation prepared in Example 3-2(containing 500mg tocopherol acetate) and commercially available tocopherol acetate tablet(containing 500mg tocopherol acetate) in an amount of 1mg/kg to experimental rats.

As a result, both of the icecream-type formulation and tablet-type formulation of tocopherol acetate showed similar blood level curve.

Acute Toxicity

Acute toxicities of icecream-type formulations of antipyretics, antibiotics, and vitamins prepared in Examples 1, 2 and 3 were investigated by employing 5 sets of male and female rats, which revealed that no mortal rat was detected up to the level of 5g/kg/day which is 500 times of antipyretics, 5000 times of antibiotics and 50000 times of vitamins in terms of their effective amounts.

The icecream-type formulation of present invention which comprises antipyretic, antibiotic, or vitamin as an active ingredient is formulated for orally applicable purpose, in accordance with the conventional formulating method by containing surfactants, excipients, tinctorials, stabilizers, buffers, suspensions, isotonic solution, and other additives, organic or inorganic carriers.

The icecream-type formulation may be administered to children in an oral dosage in an amount of 2 to 20mg/kg(20kg as a standard weight), while it may be varied depending on the type of drugs, medical treatments, diseases, patient's age and duration of medication.

As clearly illustrated and demonstrated as above, the present invention provides an icecream-type pharmaceutical formulation and a process for preparing the same. Icecream-type pharmaceutical formulations prepared by the invention have higher drug compliance to children with easy administration and good absorption and thus may substitute for troches.

Although the preferred embodiments of the present invention have been disclosed for illustrative purpose, those who are skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

WHAT IS CLAIMED IS:

1. An icecream-type pharmaceutical formulation.

2. The icecream-type formulation of claim 1, wherein the drug is antipyretic, antibiotic or vitamin.

3. The icecream-type formulation of claim 2, wherein the antipyretic is selected from the group consisting of acetaminophen, aspirin, ibuprofen, ketoprofen and isopropylantipyrin.

4. The icecream-type formulation of claim 2, wherein the antibiotic is selected from the group consisting of amoxicillin, ampicillin, erythromycin, lincomycin and cefalexin.

5. The icecream-type formulation of claim 2, wherein the vitamin is retinol acetate, cholecalciferol, tocopherol acetate, ascorbic acid, thiamine nitrate, riboflavin, pyridoxine hydrochloride, nicotinamide, cyanocobalamin or mixture thereofs.

6. A process for preparing icecream-type pharmaceutical formulation, which comprises the steps of: mixing egg yolk and milk with stirring until they are completely mixed; whipping cream and mixing it with the mixture in a volume ratio of 9:1 to 5:5; adding drugs into the said mixture in a ratio of 0.1 to 20wt% and blending them; and, putting them into an icecream maker and formulating into a pharmaceutical formula.

7. The process of claim 6, further comprising a step of mixing sugar and/or cocoa with the egg yolk and the milk.

8. The process of claim 6, wherein the egg yolk is substituted with coconut hard fat.

9. The process of claim 6, wherein the milk is substituted with soy bean milk or processed skim milk.

10. The process of claim 6, wherein the cream is carboxymethylcellulose(CMC) solution or emulsion cream which is obtained by the centrifuge of animal/vegetable oil.

11. The process of claim 6, wherein the drug is antipyretic, antibiotic or vitamin.

12. An icecream-type formulation containing antipyretic prepared by the process of claim 6, which comprises 3.0 to 18.0wt% of sugar, cocoa, egg yolk, and cream per each; 0.2 to 10.0wt% acetaminophen; and, milk.

13. An icecream-type formulation containing antibiotic prepared by the process of claim 6, which comprises 3.0 to 18.0 wt% of sugar, cocoa, egg yolk, and cream per each; 0.2 to 10.0w% amoxicillin; and, milk.

14. An icecream-type formulation containing multi-vitamin prepared by the process of claim 6 which comprises 3.0 to 18.0wt% of sugar, cocoa, egg yolk, and cream per each; 0.002 to 0.1wt% retinol acetate; 0.0004 to 0.02wt% cholecalciferol; 0.02 to 1.0wt% tocopherol acetate; 0.04 to 2.0wt% ascorbic acid; 0.0008 to 0.04wt% thiamine nitrate; 0.0008 to 0.04wt% riboflavin; 0.0012 to 0.06wt% pyridoxine hydrochloride; 0.008 to 0.4wt% nicotinamide; 0.000004 to 0.0002 cyanocobalamin; and, milk.

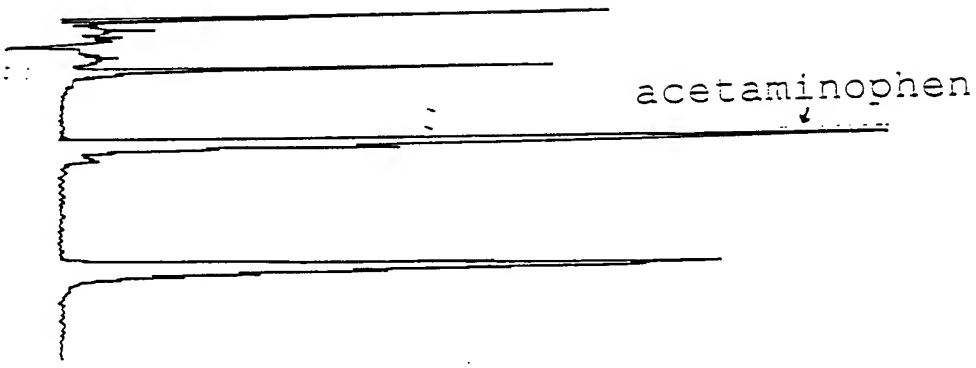


Fig. 1

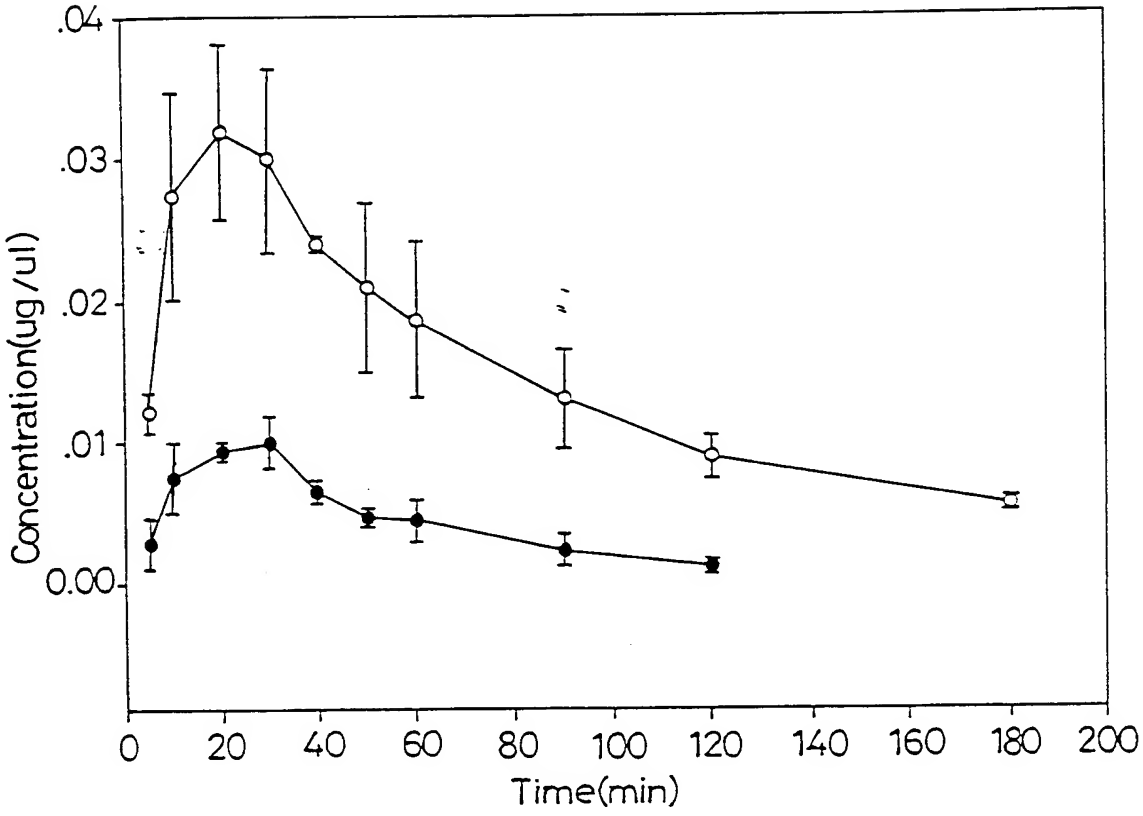

.04
.03
.02
.01
0.00
Concentration(ug/ul)
0
20
40
60
80
100
120
140
160
180
200
Time(min)

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/00321

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

Korean Patents and applications for inventions since 1975
Korean Utility models and application for Utility models since 1975

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the internnational search (name of data base and, where practicable, search trerms used)

CA ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JONES, RUSSELL et al. ' Pellet formulation provides alternative methods of administration of sustained-release morphine sulfate' In Chemical abstracts, 1996, 125:256977.	1- 14
Y	WO 94-9758 A1 (KONTOS) 11. May 1994 (11. 05. 1994) see the entire document	1-14
Y	WO 97-34496 A2 (KONTOS) 25. September 1997 (25. 09. 1997) see the entire document	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 AUGUST 2000 (01.08.2000)	04 AUGUST 2000 (04.08.2000)

Name and mailing address of the ISA/KR
Korean Industrial Property Office
Government Complex-Taejon, Dunsan-dong, So-ku, Taejon
Metropolitan City 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
YOON, Kyoung Aei
Telephone No. 82-42-481-5609

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/00321

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 94-9758 A1	11. 05. 1994	EP 625042 A1	23. 11. 94
		GR 1001437 B	30. 12. 93
		US 5525352 A	28. 06. 94
WO 97-34496 A2	25. 09. 97	WO 97-34496 A3	20. 11. 97